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# Mortality of Inherited Arrhythmia Syndromes

## Insight Into Their Natural History

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**Background**—For most arrhythmia syndromes, the risk of sudden cardiac death for asymptomatic mutation carriers is ill defined. Data on the natural history of these diseases, therefore, are essential. The family tree mortality ratio method offers the unique possibility to study the natural history at a time when the disease was not known and patients received no treatment.

**Methods and Results**—In 6 inherited arrhythmia syndromes caused by specific mutations, we analyzed all-cause mortality with the family tree mortality ratio method (main outcome measure, standardized mortality ratio [SMR]). In long-QT syndrome (LQTS) type 1, severely increased mortality risk during all years of childhood was observed (1–19 years), in particular during the first 10 years of life (SMR, 2.9; 95% CI, 1.5–5.1). In LQTS type 2, we observed increasing SMRs starting from age 15 years, which just reached significance between age 30 and 39 (SMR, 4.0; 95% CI, 1.1–10.0). In LQTS type 3, the SMR was increased between age 15 and 19 years (SMR, 5.8; 95% CI, 1.2–16.9). In the SCN5A overlap syndrome, excess mortality was observed between age 10 and 59 years, with a peak between 20 and 39 years (SMR, 3.8; 95% CI, 2.5–5.7). In catecholaminergic polymorphic ventricular tachycardia, excess mortality was restricted to ages 20 to 39 years (SMR, 3.0; 95% CI, 1.3–6.0). In Brugada syndrome, excess mortality was observed between age 40 and 59 (SMR, 1.79; 95% CI, 1.2–2.4), particularly in men.

**Conclusions**—We identified age ranges during which the mortality risk manifests in an unselected and untreated population, which can guide screening in these families. (*Circ Cardiovasc Genet.* 2012;5:183–189.)

**Key Words:** arrhythmia ■ long-QT syndrome ■ Brugada syndrome ■ catecholaminergic polymorphic ventricular tachycardia ■ mortality ■ pedigree ■ natural history

The molecular genetic substrate of various inherited arrhythmia syndromes has been identified in recent years.<sup>1</sup> As a result, an increasing number of mutations in mostly symptomatic probands has been identified. This has facilitated genotyping of family members and identification of mutation carriers before they develop symptoms. In symptomatic, untreated patients, the risk of sudden cardiac death (SCD) is substantial; however, in asymptomatic mutation carriers, the risk is ill defined. Preventive lifestyle advice may be given and pharmacological and invasive treatment offered. However, such therapies may have side effects and a significant impact on quality of life.<sup>2,3</sup> A number of pressing questions remain unanswered. Should all asymptomatic carriers of a disease-causing mutation be treated? If so, at which age should treatment be started, and from what age onward can treatment be safely withheld in asymptomatic patients?

What are the optimal genetic and cardiological screening strategies?

### Clinical Perspective on p 189

To address these issues, data on the natural history of the disease are required, but they are scarce because published studies have a strong bias toward symptomatic patients.<sup>4</sup> Therefore, we investigated the mortality with the family tree mortality ratio (FTMR) method<sup>5–7</sup> in 6 major autosomal-dominant inherited arrhythmia syndromes caused by specific mutations, including long-QT syndrome types 1, 2, and 3 (LQTS1, LQTS2, LQTS3), Brugada syndrome, SCN5A overlap syndrome (LQTS3/Brugada syndrome/conduction disease),<sup>8</sup> and RYR2-related catecholaminergic polymorphic ventricular tachycardia (CPVT). This method allowed us to study mortality in times when the disease was not known and

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therapy was not available and, thus, provided information on the natural course of the disease.

LQTS is characterized by a prolongation of the QT interval on the ECG and is associated with torsades de pointes ventricular tachycardia and ventricular fibrillation. The estimated prevalence of LQTS is 1:2000.<sup>9</sup> The 3 most prevalent (sub-)types are LQTS1, LQTS2, and LQTS3, which are caused by mutations in the *KCNQ1*, *KCNH2*, and *SCN5A* genes, respectively. Although cardiac events may occur from infancy through middle age, they are most common from the preteen years through the 20s. Patients with LQTS1 exhibit a high rate of cardiac events during childhood and adolescence, but the incidence of death is similar in all 3 types at  $\approx 4\%$  before age 40 in patients and their relatives.<sup>4,10–12</sup> CPVT is associated with adrenergically induced ventricular tachyarrhythmias. The first studies on CPVT reported high mortality rates in children. More recent studies, however, showed a later onset of SCD, where 30% to 50% of SCD occurs at age 30 to 40 years when untreated.<sup>13–18</sup> In Brugada syndrome, malignant events can occur at all ages, with a peak around the fourth decade of life. There is a striking male-to-female ratio of 8:1.<sup>19,20</sup> In the present study, we assessed the mortality of these inherited arrhythmia syndromes by studying mutation carriers at a time when the disease was not yet known and untreated.

## Methods

### Identification of Mutation Carriers and Reconstruction of Family Trees

We reconstructed large family trees of patients seen in the genetic testing program of inherited arrhythmia syndromes at our cardiogenetics department. For 5 inherited arrhythmia syndromes (LQTS1, LQTS2, LQTS3, CPVT, and *SCN5A* overlap syndrome), the first step was to search for sets of at least 2 clinically affected probands who carried the same mutation. Sets of probands with an (almost) identical haplotype (and a large likelihood of having a distant common ancestor) were selected for further genealogical analysis. Genealogical analysis was conducted until a shared distant pair of ancestors was identified. Subsequently, family trees were reconstructed by tracing the descendants of these pairs of ancestors and including all siblings in each generation. Thus, these family trees contained certain (genotyped or obligate) mutation carriers and those with a 50% chance of being a carrier (siblings of certain carriers). Furthermore, in some family trees, the additional transmission lines of the specific mutation through the family trees were identified by testing living descendants. In this way, we reconstructed large family trees of families with the following mutations: c.565G>A (p.Gly189Arg) in *KCNQ1* (LQTS1); c.296A>C (p.Tyr99Ser) in *KCNH2* (LQTS2); c.5302A>G (p.Ile1768Val) in *SCN5A* (LQTS3); c.5385\_5387dup (p.1795insAsp), a Dutch founder mutation in *SCN5A* (*SCN5A* overlap syndrome; LQTS3/Brugada syndrome/conduction disease)\*; and c.1258C>T (p.Arg420Trp) in *RYR2* (CPVT). For Brugada syndrome, we further collected 37 small contemporary family trees (the proband with all first-degree relatives) with a mutation in *SCN5A* (online-only Data Supplement Table). Some family trees were extended by testing the specific mutation through the pedigree.

Subsequently, from all individuals in the family trees, data on birth and death were obtained from official Dutch archives. In The Netherlands, these data are very well preserved from the beginning of the 19th century (1811) and have been collected of all inhabitants.

We excluded all probands because they had to be alive to visit our cardiogenetics clinic and would therefore introduce bias to years without deaths. The years of life of the parents before birth of the (obligate) mutation carriers were excluded to avoid reproduction bias

because they must have been living until this age to transmit the mutation to their offspring. We excluded the first year of life of all individuals from all the analyses because registration of neonatal mortality in the 19th century might not have been accurate. We ended all analyses at death, when a diagnosis was made in an individual (and treatment was started), or in the year when the mutation was identified (and when presymptomatic testing became available and treatment could have been started). All probands gave informed consent to the study.

### Statistics (FTMR Method)

The mortality in the family trees (observed mortality) was compared to the mortality of the general Dutch population (expected mortality) standardized for age, sex, and calendar period, as previously described.<sup>5–7,21,22</sup> The ratio of observed-to-expected mortality is the standardized mortality ratio (SMR). The expected mortality was calculated by multiplying the total number of years lived by the study population in each calendar period per sex and age category with the age- and sex-specific mortality rates of the Dutch population for each calendar period, which were available at Statistics Netherlands using the computer program Person-Years.<sup>23</sup> The 95% CI of the SMR was calculated assuming a Poisson distribution of the observed number of deaths and by using exact limits.

We analyzed the following arbitrary age categories: from 1 to 19, 20 to 39, 40 to 59, 60 to 79, and 80 to 109 years. These 20-year categories were chosen to avoid relatively empty cells and to enable comparison with similar data in the literature. In addition, we showed relevant smaller age categories in an inset when (significantly) increased mortality was observed in these specific age categories.

## Results

### Family Trees

Five large family trees were reconstructed, dating back to the 18th and 19th centuries (Figure 1, online-only Data Supplement Figure). Furthermore, 37 small family trees (Brugada syndrome) were reconstructed, comprising 508 (246 male, 262 female) relatives. The Table gives an overview of the characteristics of the family trees.

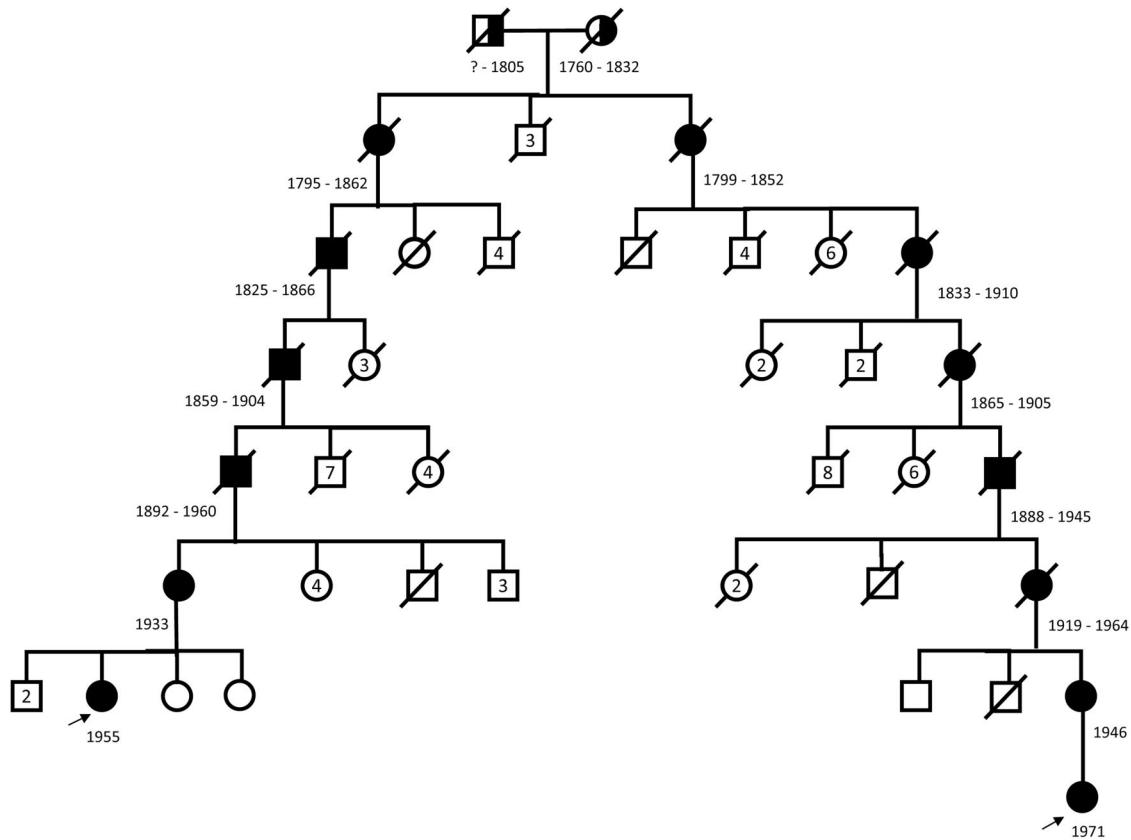
### Mortality Risk

#### *Long-QT Syndrome Type 1*

Between 1811 and 2001 (when the mutation was detected in the family), 45 deaths (between age 1 and 109 years) occurred in 2533 person-years among 59 persons. The overall SMR was 1.5 (95% CI, 1.1–2.0). In particular, we observed significant and severe excess mortality from age 1 to 19 years (SMR, 3.0; 95% CI, 1.7–5.0) (Figure 2A). Additional analyses identified a smaller specific age category in which the excess mortality was significant (Figure 2A, inset). Between age 1 and 9 years, the SMR was 2.9 (95% CI, 1.5–5.1), and between 10 and 19 years, the SMR was high (3.4; 95% CI, 0.7–9.9) but not statistically significant.

#### *Long-QT Syndrome Type 2*

Between 1852 and 2003, 25 deaths occurred in 3728 person-years among 78 persons. The mean SMR over that period was 0.9 (95% CI, 0.6–1.3); that is, there was no overall excess mortality. Between age 1 and 14 years, there were no observed deaths. From age 15 years, the SMR started to increase (15–19 years SMR, 2.6; 95% CI, 0.1–14.7). Only between age 30 and 39 years did excess mortality reach significance (SMR, 4.0; 95% CI, 1.1–10.0) (Figure 2B).



**Figure 1.** Family tree with long-QT syndrome type 1. The probands are indicated with an arrow. Solid squares indicate 100% (obligate) male carriers; open circles, female family members with a 50% probability of carriership; semisolid square or circle, male or female family member with a 50% probability of carriership (ancestor pair). The numbers in the open circles or squares indicate the total number of siblings. Crossed off family members have passed away.

### Long-QT Syndrome Type 3

Between 1811 and 2004, 32 deaths occurred in 2216 person-years among 44 persons. The mean SMR was 1.0 (95% CI, 0.7–1.4). When looking at smaller age categories, there was severe excess mortality between age 15 and 19 years (SMR, 5.8; 95% CI, 1.2–16.9) (Figure 2C, inset).

### SCN5A Overlap Syndrome

Between 1811 and 1998, 92 deaths occurred in 10 510 person-years among 308 persons. The SMR was 1.5 (95% CI, 1.2–1.8). A closer look revealed that severe excess mortality started after age 10 years (10–14 years SMR, 9.8; 95% CI,

4.2–19.2) and peaked between 20 and 39 years (SMR, 3.8; 95% CI, 2.5–5.7). Over age 60, no excess mortality was observed (Figure 2D).

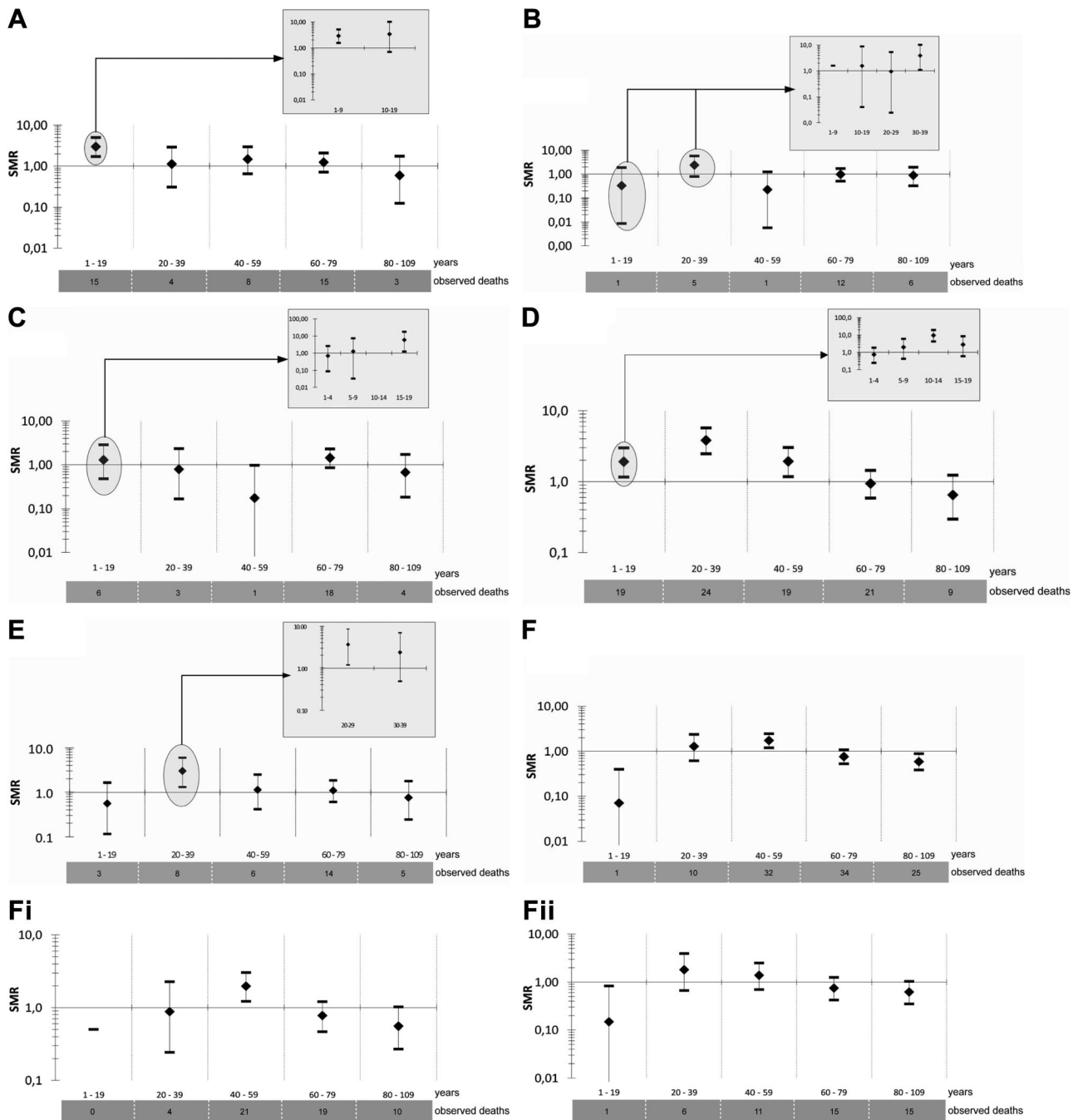
### Catecholaminergic Polymorphic Ventricular Tachycardia

Between 1858 and 2004, 36 deaths occurred in 6362 person-years among 173 persons. The overall SMR was 1.1 (95% CI, 0.8–1.5). In the age category of 20 to 39 years, significant excess mortality was observed (SMR, 3.0; 95% CI, 1.3–6.0). When looking at smaller age categories (Figure 2E, inset) between 20 and 29 years, the SMR was more severely

**Table. Family Tree Characteristics**

	Mutation	Origin of the Family Tree	Included Persons	Certain (100%) Carriers	50% Carriers	Female Sex	Male Sex	No. Deaths	Person-Years	Overall SMR (95% CI)
LQTS1 ( <i>KCNQ1</i> )	c.565G>A (p.Gly189Arg)	1760	59	11	48	27	32	45	2533	1.5 (1.1–2.0)
LQTS2 ( <i>KCNH2</i> )	c.296A>C (p.Tyr99Ser)	1852	78	16	62	34	44	25	3728	0.9 (0.6–1.3)
LQTS3 ( <i>SCN5A</i> )	c.5302 A>G (p.Ile1768Val)	1758	44	9	35	23	21	32	2216	1.0 (0.7–1.4)
SCN5a overlap syndrome ( <i>SCN5A</i> )	c.5385_5387dup (p.1795insAsp)	1803	308	32	276	160	148	92	10 510	1.5 (1.2–1.8)
CPVT ( <i>RYR2</i> )	c.1258C>T (p.Arg420Trp)	1858	173	77	96	90	83	36	6362	1.1 (0.8–1.5)
Brugada syndrome ( <i>SCN5A</i> )	Different mutations (online-only Data Supplement Table)	1877	508	121	387	262	246	102	22 150	0.8 (0.7–1.0)

SMR indicates standardized mortality ratio; LQTS1, LQTS2, LQTS3, long-QT syndrome types 1, 2, and 3; CPVT, catecholaminergic polymorphic ventricular tachycardia.



**Figure 2.** All-cause mortality (SMR) with 95% CIs by age category and male and female sex. **A**, Long-QT syndrome (LQTS) type 1. In the inset, smaller age categories are depicted. **B**, LQTS type 2. **C**, LQTS type 3. **D**, SCN5A overlap syndrome. **E**, Catecholaminergic polymorphic ventricular tachycardia. **F**, Brugada syndrome in male subjects (i) and female subjects (ii). SMR indicates standardized mortality ratio.

increased (3.7; 95% CI, 1.2–8.6). Over age 40, no excess mortality was observed (Figure 2E).

#### Brugada Syndrome

Between 1877 and 2009, 102 deaths occurred in 22 150 person-years among 508 persons. The SMR was 0.8 (95% CI, 0.7–1.0). From age 40 to 59 years, we observed significant excess mortality (SMR, 1.72; 95% CI, 1.2–2.4). When looking at smaller categories, between age 40 and 49 years, an SMR of 2 just reached significance (95% CI, 1.05–3.4). When looking at sex, in men aged 40 to 59 years, the SMR

was 2.0 (95% CI, 1.2–3.0); in females, no excess mortality was observed in any age category (Figure 2F).

#### Discussion

For most arrhythmia syndromes, it is not well-known to what extent asymptomatic carriers are at risk for SCD. At the same time, physicians face an increasing need for data about the natural history when decisions about preventive measures and screening strategies have to be made for a rapidly increasing number of asymptomatic gene carriers. The FTMR method



offers the unique possibility to study the mortality of inherited arrhythmia syndromes at a time when the disease was not known and patients received no treatment. Unfortunately, the design of the present mortality study does not allow extrapolation to the morbidity from these disorders.

We realize that we studied specific mutations in a number of families and that the results cannot be generalized to all families with these inherited arrhythmias. Yet, in syndromes where classes of mutations share pathophysiological mechanisms, FTMR data on one of them may be relevant to the larger group. In line with this, it has been shown that biophysical function, location, and type of *KCNQ1* mutations are important independent risk factors influencing the clinical course of a disorder,<sup>24,25</sup> and comparable data as to location and type of *KCNH2* mutations have been presented.<sup>26</sup> Ideally, more large families should be studied with the FTMR method to obtain evidence if the present results can be generalized, and consortia should be formed to cluster the data of pedigrees with identical mutations to study the effect of genetic modifiers on the burden of these disorders.

When interpreting the present results, one must take into account that as a result of analyzing complete sibships (certain carriers and all siblings) in each generation, the estimates express at least 50% of the excess risk, implying that the excess mortality in certain carriers is even higher than the increased SMRs that we found. However, if the reported observed SMRs are (around) 1, the SMR of certain carriers can only also be 1 because the SMR of the general population is 1.

We excluded the first year of life of all individuals from all the analyses because registration of neonatal mortality in the 19th century might not have been accurate. As a consequence, we could not analyze sudden infant death syndrome. We observed clear excess mortality in the families relative to the Dutch population, especially in young age categories in some arrhythmia syndromes. For this reason and because the analyses were based on age-specific rates, the analyses are unlikely to have been affected by a competing risk (ie, mortality from other causes in the past, mainly infectious diseases, was so high that people died of other causes before they could die of the arrhythmia syndromes).<sup>27</sup>

We identified specific age categories in patients with LQTS1, LQTS2, LQTS3, SCN5A overlap syndrome, CPVT, and Brugada syndrome to which the excess mortality was limited. These age categories compare well from what is known from data on predominantly symptomatic probands. In LQTS1 [caused by the c.565G>A (p.Gly189Arg) mutation], severe increased mortality during childhood was observed (age 1–19 years), particularly during the first 10 years of life (Figure 2A). In LQTS2 [caused by the c.296A>C (p.Tyr99Ser) mutation], we observed increasing SMRs starting from age 15 years, which just reached significance between 30 and 39 years. In LQTS3 [caused by the c.5302A>G (p.Ile1768Val) mutation], SMR was increased between 15 and 19 years. Taking into account the considerations discussed previously, these data (the first in our knowledge to be based on data in times when the disease was not known and therapy was not available) show that these patients with LQTS1 are mainly at risk before age 20 years

(more particularly, age 10 years) and in patients with LQTS2 and LQTS3, from puberty onward. In contrast to children and adolescents, adults aged >40 years in the present LQTS1, LQTS2, and LQTS3 families had no excess mortality. Persons with SCN5A overlap syndrome demonstrated significant and severe excess mortality between age 10 and 59 years, with a peak between 20 and 39 years. In CPVT [caused by the c.1258C>T (p.Arg420Trp) mutation in *RYR2*], excess mortality was restricted to age 20 to 39 years (particularly, age 20–29 years). In Brugada syndrome (caused by multiple mutations), excess mortality was restricted to age 40 to 59 years, particularly in men.

There is little doubt that the International LQTS Registry of probands and present-day relatives has been instrumental in the current knowledge of the risk of patients with LQTS. Genotype-specific risk for symptoms, including aborted cardiac arrest and SCD, have been published for different age categories.<sup>10,12,28,29</sup> Comparable with the present FTMR data, patients with LQTS1 have been reported to have the highest risk of cardiac events during childhood and adolescence, whereas patients with LQTS2 maintain a high event rate throughout adulthood.<sup>10</sup> When limited to death (the parameter studied by the FTMR method) or cardiac arrest, patients with LQTS1 are also more severely affected before puberty, whereas casualties in the LQTS2 and LQTS3 population are more prevalent during or after puberty.<sup>12</sup> However, in a larger, more recent series of patients, when limited to life-threatening events (aborted cardiac arrest and SCD), differences among the 3 LQTS genotypes were attenuated before age 40.<sup>10</sup> Published data suggest a slightly increased risk of life-threatening events for age >18 years, particularly age >40 years, in all genotypes, with probably a greater risk in patients with LQTS2 and LQTS3.<sup>10,28,30</sup> The present data do not show an increased mortality risk for age >40 years (in patients who were untreated before that age). This can be the result of the unselected population: Patients were selected by Mendelian inheritance and not because they had a severe clinical phenotype. Alternatively, it might reflect the specific clinical course of the mutations we studied, as most literature is based on pooled patients with different mutations.

In previous studies on the clinical presentation of CPVT, the mean age of clinical presentation was 8 years. If left untreated, 80% of patients with CPVT develop symptoms (syncope, ventricular tachycardia, or ventricular fibrillation) by age 40.<sup>13–18,31</sup> The median age of lethal events was 18±8 years in a study by Priori et al<sup>16</sup> and 28 years in a study by Postma et al,<sup>18</sup> and in a recent study by Hayashi et al,<sup>17</sup> a fatal or near-fatal event occurred between age 13 and 26 years. The excess mortality between age 20 and 39 years in the present study is on the late end of the age ranges described but can reflect the specific clinical course of the mutation in this family. In Brugada syndrome, the data are in line with the existing literature, reporting a peak in malignant events in the fourth decade of life, with men predominantly affected.<sup>20,32,33</sup>

These data might help to guide treatment and genetic and cardiological screening strategies in families with an inherited arrhythmia syndrome. Our best example, because of its large size, is the family with the SCN5A overlap syndrome. Based on the increased overall SMR and the mortality per age

category, cardiological and genetic screening of the first-degree family members of SCN5A overlap syndrome mutation carriers is justified from age 5 until age 60 years (the SMR starts to increase between age 5 and 9 years and is significantly increased from age 10 until age 60). Furthermore, implantation of a pacemaker or implantable cardioverter-defibrillator (which is at the moment the standard procedure in mutation carriers)<sup>34</sup> may be postponed until well after age 5 and is not needed after age 60 in asymptomatic patients not treated before. In the LQTS families, the high mortality risks at a young age justifies (active) cardiological and genetic screening of the first-degree family members of LQTS probands with the described mutations at a very young age, particularly in LQTS1. For the CPVT family, the mortality risk for ages <20 and >40 years was not statistically different from the Dutch population. Untreated asymptomatic carriers in this family, who were identified with family screening, may therefore lack an indication for treatment ( $\beta$ -blockers) at ages >40 years; hence, the present data do not support the advice to always start  $\beta$ -blocker treatment in carriers of the c.1258C>T mutation, even when there is no history of cardiac events and no arrhythmias on stress testing.<sup>35,36</sup> We emphasize that our advice does not account for other families where CPVT is caused by a different *RYR2* mutation. In Brugada syndrome, the data are pertinent to >1 mutation and accurately follow the known clinical presentation; hence, insight into the mortality of the disease warrants an expectative policy (with proper lifestyle adjustments [ie, fighting fever]), particularly in asymptomatic female members in the first 3 decades of life.

In conclusion, using the unique FTMR method, we studied all-cause mortality and quantified the risk for death in the main inherited arrhythmia syndromes by collecting data from a time when these diseases were unknown and patients were not treated for the disease. As such, we were able to describe the natural history of these diseases caused by specific mutations. We identified age ranges during which the risk for lethal events is increased in untreated patients. The data might help to further guide screening and treatment strategies in an increasing group of asymptomatic mutation carriers detected through molecular genetic testing in families with an inherited arrhythmia syndrome.

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### Disclosures

Dr Wilde is a member of the advisory board of PGxHealth.

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### CLINICAL PERSPECTIVE

For most arrhythmia syndromes, the risk of sudden cardiac death for asymptomatic mutation carriers is ill defined. Data on the natural history of these diseases are, therefore, essential for clinicians. The family tree mortality ratio method offers a unique opportunity to study the natural history at a time when the disease was not known and patients received no treatment (in large pedigrees tracing back many generations). In 6 inherited arrhythmia syndromes (3 long-QT syndrome subtypes, SCN5A overlap syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome) caused by specific mutations, we analyzed all-cause mortality with the family tree mortality ratio method, with the main outcome measure being the standardized mortality ratio. In all arrhythmia syndromes, excess mortality was observed in specific age categories. For these families, this information can be directly translated into clinical practice through guiding genetic and cardiovascular treatment and screening. For example, for the long-QT syndromes, excess mortality was observed in young age categories, particularly in type 1. We therefore advise starting genetic screening and cardiovascular screening of the first-degree family members at a very young age. In an SCN5A overlap syndrome family, excess mortality is from age 10 to 60 years (but starts to increase from age 5 years); therefore, implantation of a pacemaker may be postponed until well after age 5. For Brugada syndrome families, excess mortality was observed between age 40 and 59 years, especially in men. This finding warrants an expectant policy, particularly in asymptomatic female members in the first 3 decades of life.